Rita Levi-Montalcini’s first intellectual emigration and her research in the laboratory “à la Robinson Crusoe”: the letters from Brussels and a “Wiggish” recollection

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Abstract. This article deals with the first part of the research eventually leading Rita Levi-Montalcini to her discovery of the Nerve Growth Factor (NGF), and particularly with the experiments carried out, in collaboration with her mentor, Giuseppe Levi, during the last world war period, in the laboratory as “à la Robinson Crusoe” that she had set up at her home in Turin. In her various recollections of the NGF discovery path, Rita regarded those experiments as an heroic and revolutionary research period of her scientific life. Nevertheless, at the time they did not appear to her innovative enough such to change immediately the ordinary research program she was pursuing in the pre-war period. We argue that Rita’s narration of her initial experiments reflects a somewhat Wiggish attitude, and we discuss the possible reasons underlying her stance.

In a previous article published in this journal, I have analysed the initial period of the neuroembryological researches carried out by Rita Levi-Montalcini at the University of Turin, at first in the Anatomical Institute and, afterwards, in the Clinic of Neurological and Mental Diseases, before her forced emigration to Belgium because of the so-called “racial laws” (1). As previously said, these laws, promulgated by the fascist regime in 1938, led to the expulsion, from the university, of numerous Jewish professors and students. Among the professors evicted was Rita’s teacher, Giuseppe Levi, one of the most prominent biologists of his era. Among the students or young researchers obliged to leave the University was Rita’s cousin and classmate, Eugenia Sacerdote, and Salvatore Luria, also a classmate in the medical course (who left Italy soon and would change his proper name in Salvador, once established definitely in the U.S.A.). Luria would be awarded the Nobel Prize in 1969 for his studies on bacterial genetics. There was, moreover, also Hertha Meyer, a young German laboratory technician (already mentioned in the previous article), from whom both Rita and Eugenia had learned the method of cell cultures in vitro. Hertha, who would leave Italy in January 1939 with the help of Rita, had arrived in Turin in 1933, on the run from her home country because of the German racial laws promulgated in 1933 by the Hitler regime. (see ref. 2)

When racial laws were decreed in Italy, Rita was conducting very promising neuroembryological research in the Neurological Clinic of Turin, in collaboration with Fabio Visintini, a young neurologist particularly expert of electrophysiology. (see refs. 1-3)

As mentioned in the previous article, Rita and Visintini were obliged to publish their paper in extenso in a Swiss scientific journal, because, among the many prohibitions imposed on Jew, there was also the impossibility of authoring articles published in Italian journals (ref. 4).

We have already said that, after the exclusion from the university, Rita considered various possibilities for her future life and research path. Being more
or less equally attracted – as she would say in her later recollections – by experimental research and clinical practice in the neurological medicine, she considered the possibility of practicing private medicine (the only option open to Jewish doctors). Eventually she chose an opportunity offered by a Belgian institution where research and clinical practice went along, the *Centre neurologique* of Brussels, an establishment that – as the Turin Anatomical Institute – belonged to the network funded by the Rockefeller Foundation.

The *Centre neurologique* was a private institution founded in 1925 by Léon Laruelle, a clinician with strong interest into experimental science. It would become one of the main centres of the development of neurological research in Belgium. The decision of Rita, who was reluctant to leave the family for long periods and go to distant countries, was favoured by the presence in Belgium of her older sister Anna (Nina). Together with her husband, Ulrico Montalcini, and their three children, Nina had emigrated to Westende, on the Flemish coast. Moreover, also Rita’s teacher, Giuseppe Levi, was staying in Belgium, although not in Brussels. Thanks to a grant of the Francqui Foundation of Brussels, he had been offered research facilities at the Institute of Pathological Anatomy of Liege directed by Jean Firket (see ref. 2).

*The letters from Belgium and a life commitment to experimental research*

Until very recently little information was available on the Rita’s life and research on the period spent in Brussels, which lasted about nine months, from March until December 1939. In her main autobiography, *Elogio dell’Imperfezione* (written soon after the Nobel Prize award and published in 1987 – and afterwards translated into various languages) she did not deal with her experiments in Laruelle’s institute (ref. 5). She dwells almost exclusively on the bad weather and the sense of anguish that dominated the Belgians on the imminence of a new war. This was sharply felt, particularly by the older Belgian people, those who had suffered the consequences of the German invasions a few decades earlier. Rita also alludes with a certain humour to her weekend visits to Giuseppe Levi in Liege, where the two used to make long walks together, likely to discuss about science and the present political situation.

It is almost exclusively from the letters recently discovered by Piera Levi-Montalcini among the papers of her aunt that Rita writes to the members of the family remained in Italy (her mother, Adele, her brother Gino and her twin sister Paola) that we are now able to reconstruct some circumstances of this period in her life. Although – as we shall see now – the Belgian period was largely deceiving for the young scientist from the point of view of her experimental activity, it was nevertheless very important for her personal maturation, and especially for her professional orientation toward a life entirely dedicated to science.

In the first of these letters, dated May 29th 1939, and written from the house of Nina in Westende, Rita says that she had been the day before in Liège to meet Levi and show him her histological preparations. After reassuring the family about her health conditions, she adds that she will go as usual to the Institute (evidently the *Centre neurologique* in Laruelle) where “the work is going very well”. She adds that she has asked Visintini, her collaborator at the Clinic for Neurological and Mental Diseases, in Turin, to let the family have her “very delicate preparations”. These should be sent to her, appropriately packaged, in the trunk that the family is preparing for shipping. In the same trunk she asks, in addition to summer and winter clothes, some medical books, a clue perhaps to the fact that Rita intends to follow at least in part also the clinical activity that is component of the hospital routine of the *Centre neurologique*.

In the next letter, dated 30th July, and sent from Brussels, she says she had been in Paris, and – for the first time – she mentions “the Reumont”, that is Marguerite Reumont, Laruelle’s assistant, with whom she is evidently about to collaborate in the experimental laboratory attached to the *Centre neurologique*. She

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1 - In the *Elogio* Rita says that during the Belgian period she received every day a letter from a suitor Germano Rondolini, also a student in Levi’s Institute, who had declared his love for her after the promulgation of racial laws asking her to marry him. It is possible that Rita, who was reluctant to accept the bonds of a marriage, had decided to emigrate also to avoid the prospect of an immediate engagement with him. Together with Rita’s brother Gino and her twin sister Paola, Germano accompanied Rita on March 1939, in her emigration train journey to Belgium, as far as the France-Italy frontier in Bardonecchia.
adds, however, that because of problems concerning the technicians, “the laboratory is in a rather shabby situation”. Rita then concludes by saying: “As for me, I expect to do just the bare minimum as I am far from the laboratory in spirit”. We do not know the reasons for this attitude, but it is certain that the research carried out in the immediately following period, in collaboration with Reumont, did not produce particularly significant results.

In the letter dated 21st July, the notes of pessimism on scientific activity are in fact more evident. Addressing herself in particular to her brother Gino, Rita writes: “enthusiasm has suffered a major collapse, and I have well-founded doubts about my scientific activity and the need for doing it”. She adds that “in any case” she has meanwhile “returned to the laboratory” (evidently after a prolonged absence, perhaps due – at least in part – to a recent trip to Paris). Then she writes:

In my absence, nothing, of what I had planned, has been done and therefore the work for Copenhagen will not be ready. At least as I had planned it. This has given me great peace and joy. Tomorrow I will see Laruelle and we will see whether to participate anyway with what done until now. Very briefly, we plan to leave.

This is a significant passage, not only because it reveals Rita’s scientific difficulties during the period in Brussels, but also because it highlights an important aspect of the mentality of the true researcher: the anguish in the face of the difficulties of experimental work comes above all from feeling himself (or herself) personally inadequate and responsible for research failures. It is attenuated when the obstacles to its development come from external sources.

The reference to Copenhagen in this passage indicates the “III International Congress of Neurology” scheduled for August 21-25 in the Danish capital, an important event in which Laruelle and his collaborators intended to take part. On the problems connected with her possible participation in this congress, Rita returns in the following letter dated 4th August. Here she highlights the insufficiency of the results she obtained in the Centre neurologique for the purpose of presenting a scientific communication, with an evident criticism of Laruelle who – in her way of thinking – is at least partly responsible for the failure to complete Rita’s studies.

Here are her words:

I live in almost complete rest. Laruelle very kindly approved my decision not to make the communication since in this last period he has prevented me from concluding my research. Instead, I will make a demonstration of my preparations. For practical purposes, this is the same as a communication, but I will not compromise myself with assertions that I may later regret. I will give the full work at the next congress. You know how indifferent that is to me.

Rita then specifies that she will leave by boat from Antwerp on August 14th. Due to the large amount of histological preparations she will be carrying for the demonstration in Copenhagen, she would be driven to the embarkation city by the “Baroness”. The personage mentioned is Agnès della Faille d’Huyss, a Belgian aristocrat, acting chairman of the board of directors of the Centre neurologique).
The next letter was written from Copenhagen on August 21st, the day of the inauguration of the congress. In this letter Rita gives some details on the official ceremony that took place in the morning “with the intervention of the King” (Christian X of Denmark). The plenary lectures were given first by Henry Dale (who had received the Nobel Prize for medicine the previous year), and “immediately after, by Laruelle who has met with a lot of approval, and impartially it must be acknowledged that he has had a real success”.

Rita continues talking about the demonstration of her histological preparations, done together with Reumont, which has also been very successful, to the point that Laruelle overtly demonstrated his satisfaction addressing her by saying repeatedly: *Ma chère amie*.

It is singular that neither in the previous letters, nor in this one concerning the demonstration given to the Copenhagen congress, Rita specifies in any way the topic of the research she is conducting in collaboration with Reumont and under the direction of Laruelle. We have a very succinct account on the theme of this research from the conference Proceedings published in the *Revue neurologique*:

M. L. LARUELLE, Mlle R. LEVI-MONTALCINI and Mlle M. REUMONT (Brussels).

The vegetative centres of the spinal cord in mammalian embryos (cat and rabbit).

Communication essentially consisting in the presentation of preparations and projections; 1° on the first bud of the vegetative centres of the spinal cord in the rabbit embryo; 2° on the modifications, according to the embryonic development, of the three intermediate groups: internal, intermediate, intermediate-external; 3° on the characters of the cells and direction of the neurites of the three groups. (ref. 6, p. 369)

The theme of the demonstration represents a meeting point between, on the one hand, the interests of the group of Laruelle and Reumont, who for some years had been studying in particular the nervous centres of the autonomic system (sympathetic and parasympathetic) and, on the other, the skills and interests of Rita. As we know, in the period with Levi in Turin she had acquired a great experience in the manipulation of embryos, although her preferred preparation was the chicken embryo (while Laruelle and Reumont studied the mammals).

During the days in Copenhagen, an event of great importance for Rita was the encounter with Giuseppe Moruzzi, a young physiologist who had already acquired an international renown. This is what we learn from a conference Rita dedicated to Moruzzi in Parma on March 20th 1990, four years after the death of the great physiologist.

We first met at a conference in Copenhagen on a tragically historic day: it was the first of September 1939, the day of the invasion of Danzig. Moruzzi was
just one year younger than me, he was much more handsome and attractive, and I was impressed by the fame he had earned at only 29 years of age. I was a shy young girl who had recently graduated and I was perfectly unknown to him. For racial reasons I had been expelled, or – at least – obliged to leave my country and to take refuge in Belgium where I was offered work. On the day of our chance encounter in Copenhagen, the newspaper headlines were announcing the invasion of Danzig, which meant the beginning of war. We spent all day together […]. He, like myself, was in a state of despair because of the alarming impending events, and I was struck by the serious way in which this young man faced them. Leaving aside my critical situation, the whole world was then in danger. All day along, until late evening, we discussed what could be done. Eventually, every one of us returned to their countries. […] At that time, he was working in Cambridge with Lord Adrian; the importance of their studies was already known, as I will indicate later. I went to Belgium, and from Belgium I came back to Italy when the war was nearing, and then we all know what happened. By a miracle both of us survived and we were destined to meet each other ten years later.

To get a clue as to the reasons for the decisions that Rita made after returning to Brussels, it is necessary to take into account this meeting between the two young Italian scientists. Moruzzi was then working in Cambridge with the great English neurophysiologist Edgar Douglas Adrian (Nobel Prize for Medicine in 1932). In the immediately preceding years, however, he had spent a long period working in the Laboratory of Clinical Neurophysiology of the University of Brussels to conduct research under the direction of Frédéric Bremer (a physiologist then very famous for his studies on sleep mechanisms).

Back to Brussels, on 23rd September Rita writes to the family that she could not come soon to Italy due to difficulties in obtaining the necessary visa for the return. However, she does not approach this unexpected, and apparently annoying, situation with anxiety; on the contrary, she feels herself in a condition of “complete physical well-being”. In this letter, we find a notation that – in various forms – will come back the writings of her maturity. Rita narrates that she feels the scientific work as a delight, and – at the same time – as a way of escaping the worries of everyday life: “again I am very strongly attracted by my studies and I am amazed by the complete possibility of escaping to the present, diving into the wonderful charms of nerve conduction”.

What she then writes suggests a decision likely sketched during the meeting with Moruzzi in Copenhagen, and afterwards matured in Brussels, following the difficulties of returning to Italy and her uneasy situation at the Centre neurologique, where things have come back to the ordinary and boring routine, despite the success of the Copenhagen demonstration:

On Monday I hope to be able to speak with Bremer as I told you, to see if I can work with him. He is one of the most famous living physiologists and for this reason, it would be a great fortune for me to work under his guidance. If he accepts me, I will find myself in a more awkward situation than Buridan’s ass. The infinite desire to embrace you again pushes me to neglect the long-awaited possibility of continuing my studies; on the other hand, I am discouraged by the inactivity to which, on returning, I will have to face. If
I stay, I will most likely finish the work started in the Neurological centre but, as I told you, this work interests me much less than what I could do in Bremer’s physiological laboratory. Therefore, if I am unable to work with him, I will also leave the work I started with Laruelle without much regret and will certainly decide to return.

Rita then asks her family for advice to help her in her decision, but she reassures her loved ones that, by staying in Belgium, she will not suffer loneliness due to the “infinitely dear closeness” of her sister Nina. Like many of the letters written from Belgium, this one also brings additions from Nina that fill in the empty margins left by the sister. Precisely because she imagines that the family in Italy welcomes with regret the news of the possible decision that Rita is taking to stay in Brussels, Nina intervenes on this point by writing:

Dear Ri [ta] is here reading next to me. I really wish she could remain. It is not selfishness, believe me, but I see that here she is so well, and that she is so animated for her studies that – I think – it would be really a pity to throw everything away now that we are more calm on the course done.

The next letter, dated 27th August, announces to the family the outcome of the interview with Bremer, which had been very positive despite the initially uncertain prospects outlined by the famous physiologist, due to the “greatly reduced subsidies to the laboratory” for which “it was very difficult for him to accept new applicants”. The doors of the prestigious laboratory open wide for the young Italian scientist. With reference to Bremer, Rita writes:

He received me very kindly and I spent the morning with him. Result: he proposed that I definitely start working, and declared himself truly enthusiastic about the work program I presented him and about the work done in Turin. Today with the assistant, I have begun to sketch the research plan with an assistant.

Nina intervenes again in this correspondence, undoubtedly to alleviate the disappointment of the family at the knowledge that, following acceptance in the Bremer institute, Rita will probably remain in Belgium for a long time. With a certain humour she comments on the fame enjoyed by Bremer. Of him she says that he is “such a world celebrity that even the penguins at the north pole talk about him” […] The fact that he has asked Rita to come to work with him immediately must make proud every maternal and fraternal heart. […] If you could see her animated and full of strength as she is, you would rejoice with me”.

On 6th October Rita writes again to the family saying, with reference to her new activity in the Bremer’s Institute, that she spends “the afternoons in the physiology library, studying and dreaming of beautiful research plans, which perhaps will remain dreams, but that doesn’t matter”.

From the following letter, written on 11th October, we have a first indication of the work planned in Bremer’s laboratory. This is evidently a research on chicken embryos, which, however, has a difficult start for the reasons that, she explains, with a certain humour:

I am now going to my laboratory where so far I have not been able to achieve anything because of the

Figure 5. Frédéric Bremer (1892–1982) in 1959 in his office at the University of Brussels. (© Giovanni and Paolo Moruzzi).
strike of my eggs, despite my cares more maternal than that of a hen. While waiting for the material, I spend my time studying in the library, where I find myself like a fish in water. The atmosphere is very pleasant.

The "strike" of the hens evidently ends quite soon, but new difficulties arise, as we learn from the next letter, dated October 15th.

Rita writes:

I attend the new institute assiduously but, up to now, embryos have played me bad tricks. Because of the malfunction of the thermostat, they all died before I could subject them to the experiment. Certainly, I am not discouraged for so little but I regret the lost time. The assistant and the technicians do their best to help me. I therefore hope to remedy this problem soon. Once overcome it, undoubtedly I will be confronted to more serious ones, given the difficulty of the experiences I am planning. I am – however – sufficiently stubborn and optimistic to face them.

The theme of the experimental difficulties with the eggs and embryos resurface in the following letter, written on October 15th:

Certainly I continue to fail with my eggs, but I am sure that sooner or later I will be able to overcome these stupid technical difficulties, and I am increasingly convinced that I have a very promising research field ahead of me. In addition, being able to work with Bremer is not only very pleasant for me but also very useful.

The next letter, written on November 15th, is dominated by preparations for departure which, however, cannot yet be undertaken because the visas necessary to cross the frontiers do not arrive (while the trunks are already ready). Rita too seems determined to return, following the advice received (in a previous letter) from Gino and Paola, but she cannot hold back her regret.

My Pa [ola]- and Gi [no], I listen to your advice, and I leave my chicks and – with them – all my dreams of working in the best laboratory I have found so far. My dearest ones, you will forgive me this regret, which may appear to you excessive. But, in recent months I have been through such painful moments, and I owe to this new activity – just begun – to have acquired serenity and confidence in the future. I hear my dear Gi [no] all your just objections, summed up in the detachment of the Demiurge from the troubled human affairs. Working happily without becoming slaves! Very sensible thinking, but which does not take into account the affective component of human nature. That should not be ignored too much, because – after all – it is the mainspring of all our activities and its justification.

She expresses also her regrets for not having been able to complete her research at Laruelle’s laboratory.

In the last letter sent from Belgium, dated November 17th, Rita seems to reconsider her decision to return soon to Italy, and outlines the possibility to stay another month in Brussels, in order to continue her physiological experiments, if in the meantime Bremer returns and the laboratory will be back in function. Returning home attracts her because of the possibility of hugging family members to whom she is very attached. Rita realizes – on the other hand – that in Turin she will have to face “the certainty of a situation of complete inactivity”. In contrast – as she says – in Bremer’s laboratory “I saw all my work projects come true”.

The letter ends with Nina’s usual addition, this time entirely dedicated to her sister’s condition of anxiety and indecision. It is worth transcribing it in full, also because it contains a reference to Rita’s adolescence, at the time of the girl’s decision, – against the will of the father, Adamo Levi – to resume her studies in order to have to access a professional career, a possibility generally precluded to young women:

My most beloved ones, there is no doubt that for now there is no longer any reason for apprehension here, and that perhaps Ri [ta] could still stay for a while – even if we can leave – which is not yet certain. I hope you have received our last letter, in which we talked about this possibility, and that this letter will find you prepared. It would be a matter of enabling
her to reap here what she has sown so far. Both at Bremer and at the Centre, and, above all, not to give her a big disappointment. She would return to Turin by December at the latest, full of laurels and titles for the future. Just the idea of resuming her work made her smile again on her lips and ... put her stomach back in place, which was not going too well these days. Her work is truly her reason for living, and perhaps the only reason, except for her great attachment to you and to us. I am thinking that, if our dear Dad heard me, he would say, once again, that “I put her up”, as he said me on that memorable day when I supported her – and I am proud of that – to resume her studies. My great affection for her guarantees me that anything I do or say, I do it exclusively for her good, even at the cost of taking on some small-great responsibility. Will you forgive me, my beloved ones?

We do not know if Rita and her sister’s family eventually could get the visas necessary to cross the frontiers and come back home. However, as narrates recounts in her autobiography, they succeeded in arriving to Turin, just on Christmas Eve 1939, after a lengthy and rather adventurous car journey, through the Europe devastated by the war. (Levi-Montalcini, 1987).

In conclusion, the months spent by Rita in Belgium represent a period of strong anguish and bitter disappointments. In neither of the two laboratories attended, was she able to conclude satisfactorily the research undertaken. At the Centre neurologique, where the study project was a rather conventional histological research, she certainly had difficulties, even of a personal nature, at least in the relationship with Laruelle.
Certainly, in the letters she writes, there was never any sign of appreciation for them from the human point of view. She is much more enthusiastic about Bremer, his lab, his personality, and even the research project she intends to develop with him (almost certainly based on an electrophysiological study of the developing nervous system in chicken embryos). A project that probably was linked to the one she had conducted in Turin together with Visintini, and which – as we know – she had been forced to abruptly interrupt due to racial laws, but which could have been developed in Brussels in one of the most important electrophysiology laboratories of the world.

On the other dimension, the Brussels period is extremely beneficial for Rita’s scientific and personal life. It is there that her vocation for experimental research becomes well defined and clear-cut, while – in the initial period of studies and investigation in Turin – she was divided between medical practice and laboratory research. As we have already noted, – at the time of her forced emigration, the attraction for clinical medicine had perhaps directed her towards the Centre neurologique of Laruelle, rather than toward a basic research institution. Rita’s vocational maturation is also evident from the stubborn confidence with which she faces the difficulties that hinder the course of her experiments (at Laruelle’s there are no good technicians, at Bremer’s the embryos die perhaps due to the malfunctioning of a thermostat) and – from her attitude toward the greater difficulties to come.

The return to Turin, and the advice of a new dantesque Ulysses, Rodolfo Amprino

As she was anticipating, discouragement and frustration for the forced scientific inactivity were the sentiments dominating Rita’s mood for a long period after coming back to Italy. This situation, however, will end about one year later, following a rather unexpected encounter with a former colleague at the Anatomical Institute of Turin, Rodolfo Amprino.

Rodolfo, who was not Jewish, had left Italy after the racial laws. This was because, as other loyal and affectionate collaborators of Giuseppe Levi, he was disgusted by Levi’s dismissal. Moreover, he was nauseated by the attitude of the new director of the Institute, Ferdinando Rossi, a decidedly mediocre anatomist, very close to the fascist regime. After a period spent in a laboratory in Chicago, Rodolfo had come back to Italy, and eventually, on November 1940, he visited Rita in her home at Corso Umberto of Turin.

In the Elógio Rita describes, with a certain emphasis her encounter with Rodolfo, who unexpectedly went to ask her “in a rough way ‘à la Piedmontese’ about her [scientific] projects”. Surprised as she was by Amprino’s inquiry, Rita says that she was not able to reply promptly.

And adds:

My silence provoked his abrupt and somewhat irritated reaction: ‘you don’t lose courage in the face of the first difficulties. You should set up a small laboratory and resume the interrupted research. Remember that
Cajal, in that sleepy city that must have been Valencia in the middle of the last century, built a fundamental work that laid the foundations for everything we know about the vertebrate nervous system. The suggestion could not have fallen into more prepared ground to receive it. At that moment, Rodolfo appeared to me in the guise of Ulysses, as Dante immortalized him in the XXVI canto of the *Inferno*, when he encourages his companions not to lose heart and to continue the route. In fact, he touched a chord that had vibrated in me since early childhood: the desire to explore unknown places and adventures. The jungle that presented itself to me at that moment was more fascinating than a virgin forest: it was the nervous system, with its billions of cells, aggregated in populations, each different from the other and locked in the apparently inextricable tangle of nervous circuits, intersecting themselves in all directions inside the cerebrospinal axis. Added to the pleasure I anticipated for that type of studies, there was the idea of carrying out the project in the prohibitive conditions created around us by the racial laws. If Cajal, with his giant moves and his exceptional intuition, had dared to enter that jungle, why not venture myself into the road opened by him? The first experience with Visintini had been very encouraging. (ref. 5, p. 94).

This long quotation is a typical example of the rather epic way in which, in her later recollections, Rita narrates some crucial moments of her life and experimental research during the difficult period of the war. It is written with a certain literary taste, and, in addition the reference to Dante, is largely inspired by the writings of Santiago Ramón y Cajal, the great Spanish neuroanatomist, who was also a very effective writer. Indeed Cajal’s autobiography (*Recuerdos de mi vida*), published in various editions, starting from the 1920s (and translated into various languages), had become a *livre de chevet* for many young scientists of the time. Applied to the description of the minute anatomy of the nervous system, the expressions used by Rita such as “jungle”, “virgin forest”, “apparently inextricable tangle” undoubtedly resound of some splendid passages of Cajal.

The *Elogio* was written between 1986 and 1987, and certainly reflects the state of mind of Rita after the Nobel Prize was awarded. An important reference to the meeting with Amprino, less literary but no less significant, is present in a letter that Rita wrote to Rodolfo on February 14th, 1974, with a precious indication that allows us to establish the day of the event:

> The racial laws prevented me from attending the Institute, where, on the other hand, Rossi reigned. And I remember that evening when you came to me (the same day your Father died almost suddenly) and you convinced me to organize a tiny laboratory in the house. The rest was only the consequence of your suggestion (how many times have I thought about it and with what gratitude!) and of the courage you have been able to infuse me with your words.

Lorenzo Amprino, Rodolfo’s father, died on November 13th, 1940, and therefore – if we can trust Rita’s memory (very strong, but not infallible) – then the fateful encounter, a true “turning point” of her scientific activity (as, in her letter, she defines it using the English phrase) is to be placed in the evening of this day. A day that takes place in a rather sad period for Italy, which has recently entered the conflict, after the declaration of war on France in June 1940.

*Planning a home laboratory: an affluent Jewish family and the “casalinghitudine”*

We know that Rita followed Amprino’s advice, and that this had extraordinary consequences on Rita’s future scientific career. At the time it was made, the decision to create a home laboratory for the investigation of the nervous system in the chicken embryo must undoubtedly have appeared rather unrealistic and somewhat reckless, especially considering that it was taken by a family group consisting largely of women. Rita’s father, Adamo Levi, had died in 1934 and the family was made up by her mother, Adele Montalcini, by Gino (the eldest of the children), and then by Anna (Nina, who was – as we know – married), and by Rita and her twin sister Paola. In her recollections, Rita writes that Adele had supported the choice, even if it involved significant financial costs, the most significant of which was the purchase of two Zeiss microscopes, one with low magnification for microdissection, and the other with high magnification objectives, needed
for the observation of histological slides. Gino (the first to add the mother's family name to the father's) was an architect and had great technical-manual skills. He built “a thermoregulated glass box”, with two openings that allowed the experimenter’s arms to be inserted in order to operate the embryos in an aseptic environment. This was a simple and appropriate substitute for the sophisticated culture chamber used by Rita in the anatomical institute of Turin for the studies of cell cultures, since the period of her graduation. She had been working in collaboration with her cousin and classmate Eugenia Sacerdote, under the supervision of Giuseppe Levi and Hertha Meyer. The letters from Brussels suggest that, although living in her own home, with her husband and children, also Nina undoubtedly supported Rita in her decision to set up a home laboratory.

To understand how, in the case of Rita, it was possible to implement materially Amprino’s suggestion of building a home laboratory by a predominantly female family group, we must consider the importance of women in families of Jewish descent. We must also take into account the importance of the home interior as a place of intensely lived life and a space for creativity. This is along the idea of “casalinghitudine” (from “casa”, home), a word created by Chiara Sereni to indicate the deep affection of Jewish families for the interior of their homes, the sense of protection they felt therein, and also its conception as a place for creativity, matured especially at the time of confinement within the ghetto (see refs. 8-9). We must also consider the fact that the Montalcinis were a wealthy family and could easily afford the large costs of buying expensive microscopes and other laboratory equipment. Among other things, they owned the building in Corso Umberto where many members of the family lived, and in which Rita was able to set up a first laboratory and start her research destined to have truly extraordinary developments.

The laboratory was eventually installed in Rita’s bedroom. It became soon a meeting point for her friends and colleagues that were against the fascist regime. Starting from the summer season of 1941, in her work she was helped by Giuseppe Levi. The authoritative and rather imposing master was now in the minor position of Rita’s assistant, as he would recognize in a letter to Viktor Hamburger (Rita’s mentor in the first years of emigration to the Washington University of St. Louis).

In this letter (written in German on 11th March 1959, in order to acknowledge Hamburger’s contribution to the celebration of his 85th birthday), Levi says:

> It is especially flattering for Rita and for me that a researcher like you, who is considered a great authority in the field of developmental physiology, has appreciated our findings. But I must confess that in those investigations published in 1942 my personal participation was very slight. They were done in the private apartment of Rita. I was just back from Belgium where I had undergone difficult events.

With the events of the war becoming more and more threatening for the inhabitants of Turin, from the house in Corso Umberto the laboratory would be

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**Figure 8.** A photo of 1940 with the family group who decided to set up an experimental laboratory in Rita home in Turin. From left to right: Gino, Rita, Adele and Paola Levi-Montalcini (© Piera Levi-Montalcini).
eventually transferred to Valle San Pietro, on the hills near Asti. It was installed there in the house owned by the Nina’s husband, Ulrico Montalcini (Villa Agnelli), where part of the family had taken refuge to escape the heavy bombing of the city. In that period, Rita used to come to Turin to meet Levi and discuss with him about the experiments and the way to publish the results she was obtaining. This situation lasted until the end of 1943, when – following the German invasion – both Rita and Levi (with their respective families) were obliged to go away and look for a refuge toward the south of Italy.

The research Rita carried out in her home laboratory is really of great importance and marks a change of paradigm in the history of neuroembryology (in the meaning of a famous book of Thomas Kuhn, see ref. 10). With no doubt these experiments of the war period set the stage for the future investigation of Rita, largely carried out in St. Louis, leading her and her collaborator, Stanley Cohen to the Nobel Prize.

It is not surprising, therefore, that, in her autobiographical recollections, Rita gives a particular emphasis to the history of that period of her research. She narrates the experiments with literary taste, starting from the period in which they were planned, i.e. following the reading of a paper by Viktor Hamburger, her future mentor – as we know – in St. Louis. Rita portrays the results obtained as a heroic and revolutionary achievement, and the beginning of an uninterrupted, fascinating and epic, research pathway, concluded many years afterwards with “the honours of Stockholm”. However, as we will now argue, this is not exactly the way she felt at the time she was working in her home lab, nor in the immediately subsequent years, until her emigration to St. Louis. Many clues suggest that the way she narrates the beginning of what she will call the “NGF Saga”, is largely based on a posteriori attitude (“Whiggish” according a particular acceptance of this abused word). An attitude that was the consequence of the unpredictable extraordinary developments of her 1944 experiments, and also of Rita’s new situation after the NGF discovery and – especially – the Nobel prize award.

In order to clarify this point I need to summarize and discuss here the experiments carried out by Rita and Levi during the war period, and to situate them in the appropriate historical context of the ongoing development of neuroembryology. For a more detailed account, the interested reader is referred to a recent book in which I have analysed in detail the beginnings of Rita’s scientific activity.

**The chicken embryo, Maria Lydia Shorey and the birth of modern neuro-embryology**

The research topic along which the discovery of the NGF lies corresponds to one of the fundamental problems faced by scholars since the introduction of experimental methods in the field of neuroembryology. It concerns the mechanisms that regulate, during development, the establishment of contacts between nerve cells, and between these the organs and tissues...
they innervate, both on the motor and sensory side.

A landmark study in this research path appeared in 1909, the year of Rita’s birth. The author was a young American researcher, Marian Lydia Shorey, and was based on her doctoral thesis, developed under the supervision of Frank Rattray Lillie at the Department of Zoology of the University of Chicago (ref. 11). Lillie, who had been one of the founders of the Marine Biological Center in Woods Hole, was an authority on developmental biology. He had been instrumental in contributing to introduce, in this research field, the chicken embryo as a reference preparation, especially with the publication, in 1908, of the volume, “The development of the chick, an introduction to biology”. In this book, against a consolidated tradition of research based mainly on morphological investigations, the American scholar promoted a dynamic and physiological vision of the study of development, largely based on experimental manipulations, which he defined as “developmental physiology” or “experimental embryology” (12).

Among the fundamental factors that underlie embryonic development, Lillie considered, particularly “the effects of the intraorganic environment, i.e., of component parts of the embryo on other parts”, which he indicated as “correlative differentiation”. Against a preformistic conception of embryonic growth, he assumed that – far from being programmed in every detail – the harmonic growth of organs or parts of organs is based on the reciprocal influence of neighbouring structures or in functional relationship. This integrated or “correlated” action is mainly the outcome of influences exerted through the extracellular environment.

Within these conceptual frameworks, in her PhD research carried at the University of Chicago under Lillie’s supervision, Shorey conducted a series of experiments aimed at investigating the effects of removing peripheral structures on the development of nerve cells of the spinal cord. Using fine sewing needles as electrocautery devices, she destroyed the buds of one of the two wings in the embryo (leaving the other intact as a control). Shorey found that this manoeuvre led to a reduction in the number and size of the precursors of nerve cells (neuroblasts), in particular in the motor columns of the spinal cord and in the corresponding sensory ganglia, (i.e. those normally assigned to the motor or sensory innervation of the wing). Based on a series of considerations, she interpreted these effects as due to a failure of nerve cell growth (hypoplasia), due to the lack of some influence, normally exerted by the peripheral tissues through the extracellular medium (lymph), and absent following the destruction of the wing buds.

Spemann’s pupil and an article read in a cattle car

In 1932, about twenty years after Shorey’s fundamental work, one of the students of the German embryologist Hans Spemann (who will receive the Nobel in 1935), the aforementioned Viktor Hamburger, received a fellowship from the Rockefeller Foundation to conduct research in Chicago, in the Department of Zoology headed by Lillie, Shorey’s mentor – as we

Figure 10. Marian Lydia Shorey (1873-1922). Graduation photograph from the Eastern State Normal School of Castine (Maine), 1894 (©).
know – in her doctoral dissertation. On Lillie’s suggestion, Hamburger repeated Shorey’s experiments on chicken embryos, using the more refined methods used by Spemann and collaborators in amphibians. In 1934, Hamburger published an article, largely confirming and expanding Shorey’s findings, which is particularly important to the story of NGF. This is because a copy of this work was sent by the author to Giuseppe Levi, who passed it to Rita in 1938, asking her to read it carefully and possibly check the results and conclusions. The exchange of publications between Levi and Hamburger was favoured by the fact that they were both members of the network of European scientists funded by the Rockefeller Foundation, which was then engaged in an effort to promote biomedical research worldwide.

Rita has narrated the moment in which she first happened to read Hamburger’s 1934 paper at length and with emphasis, at least in two occasions. One was in relation with the celebration of Viktor’s 80th anniversary. The written text, published in 1981, deserves an extensive quotation, both as an example of Rita’s literary talent, and also because it is relevant to the point I am raising:

I first met Viktor in a cattle car in northern Italy. It was on a day in that fateful June of 1940 when Mussolini declared war against France, which had already been stabbed to death by Hitler’s army. Sharing a train with cows was only a minor discomfort compared with those about to afflict the daily life of the Italian nation throughout a catastrophic five-year war. But, in mid-summer of 1940, Il Duce was triumphantly predicting “instant victory” over loudspeakers that blared from the Palazzo Venezia.

I was sitting on the floor of one of those railway cars, which have neither seats nor side walls with conventional doors (niceties unknown to cows) and my legs were dangling out in the open air. The train was running at a slow speed across the country between Turin and the small village I was heading for. I was young and I enjoyed the fresh air and this rather unusual and somewhat dangerous way of travelling. While contemplating the yellowing corn and the bright red poppies, I was reading a reprint lent to me by Giuseppe Levi on the effects of wing bud ex-
sible falls”.

More important is the absence in the second narrative of the critical reference – and certainly ungenerous and almost malevolent – to the fact that Levi considered a pupil nothing more than a manual instrument at the disposal of his teacher, almost lacking any thinking ability of his own. A statement completely contrary to the reality of the facts, and also to the memories of the students (including Rita herself in other places and times), since all concurs to underline Levi’s profound respect for his students and collaborators. If Levi really hinted at Hamburger’s article with some disdain, it is possible – as we will see better later – to find a scientific, and not trivial, explanation for his attitude. In fact, a master of the study of the nervous system of his level certainly could not appreciate, at least from a methodological point of view, a research like that of the young German scientist, based – as we will now see – on the use of staining techniques totally inadequate to mark nerve cells. A research, in which – according to Levi – in choosing the most suitable structures for his neuroembryological study, the author seemed to ignore even “the reasons well known by every histologist” (ref. 14, p. 539).

The reason for the absence, in the Elogio, of Rita’s criticism of Levi, as a poor estimator of the students intellectual abilities, is easily accountable for. It has to do with a chapter of the book, entitled “Farewell to a teacher and a father”, which is dedicated to Rita’s last meeting with Levi. This event took place “on an evening in late January 1965, at the San Giovanni hospital in Turin”. The teacher was then hospitalized for gastric cancer – and also for gangrene in his right foot, which was then extending to his leg – two conditions that would lead to Levi’s death within a few days (on February 3rd).

In her engaging and sympathetic narration, Rita recollects, together with Levi, the “joys and bitterness” of their intense life, the researches, the difficult moments of racial persecutions, their emigration to Belgium and the return in difficult circumstances, the experiments made together in her home laboratory in Turin. Faced with the intellectual vivacity and still youthful enthusiasm for science of the old professor (Levi was 92 years old), Rita says that she “understands the secret of the great influence he exercised on young people”. This derived from “the passion with which he had pursued his studies and directed those of his students, indifferent to the honours and applause paid to the old masters”. Compared to the deep appreciation of Levi in the “Farewell” chapter, a critical reference to Levi as poor estimator of the students in other parts of the book, similar to the 1981 narration of the “cattle car” reading, would have been ill placed in the Elogio.

With regard to this rather significant discordance between the two narrations of the event, it is significant to note that is rather common for Rita to present narrations or express judgements which can be significantly different in written or oral texts produced in various moments of her long life. Although, this can be due to rather comprehensible and ordinary reasons, there is no doubt that often she adapts with skillfulness to the circumstances, and somewhat opportunistically manipulates, her accounts of the facts narrated. As to Rita’s criticism toward Levi’s attitude with students and collaborators, although the master was known, both in family and in the laboratory for its “terrible fits of anger”, generally due to “his intolerance of the superficiality and failure to fulfil the duties entrusted to them”, he had a profound respect for their work and their personality. In fact, few Italian academics respected so deeply the work of students like Levi, who constantly wanted their scientific results to be published in their exclusive name, and was always prodigal of advices and helps towards students and collaborators.

**Viktor Hamburger and the renaissance of modern neuroembryology**

It is time now to go into the specifics of the Hamburger article, which Rita had read in such particular circumstances narrated with great vivacity (15). This article represents a milestone in the history of neurobiology, despite some undoubted flaws in the experimental approach of the young German scientist, properly emphasized by Rita and Levi in their 1942 paper. Rereading what Hamburger wrote, even many years later, it is easy to agree with Rita when she speaks of “the crystal clarity of the writing”. In fact, there is a profound rigor and systematic organization in his interpretation, analysis and discussion of the results, and in the planning of the experiments. These qualit-
ies must have attracted Rita when she read the article, in the phase of forced experimental inactivity she was then living.

As said, Hamburger carried out his experiments in Chicago, upon Lillie’s suggestion, as a check and extension of those made by Shorey in the same lab about 20 years before. He fully confirmed the previous results, with experimental concordances in some cases rather surprising, for a research made many years later, with somewhat different techniques and open to different sources of variability and uncertainty. The reduction in the number of motor cells induced by the ablation of the peripheral structure was similar. As Shorey, Hamburger also obtained a reduction – albeit less significant than his predecessor – in the development of the sensory nerves and ganglia, and of the sensory component of the spinal cord. Furthermore, using – like Shorey – a staining method based on a haematoxylin-type colour, he agreed with her in asserting on the lack of degeneration phenomena in the spinal cord, and – attributing the observed effects to a hypoplasia consequent to the removal of peripheral structures.

The difference between Hamburger and Shorey concerned mainly the interpretation of the effects observed. This depended on an aspect that the German scholar emphasized in his paper. The degree of hypoplasia observed in the spinal nerve cells did not exclusively depend in a quantitative way on the mass of the removed peripheral structures. It had also a qualitative specificity, in the sense that there was more marked hypoplasia in the motor cells of the cord if the removed part contained a greater muscle mass. If more proportion of the skin was removed, the hypoplasia concerned more the sensory structures.

Based on these observations, Hamburger considered unlikely an explanation – as that invoked by Shorey – relying on a generic chemical-metabolic action exerted by peripheral structures on spinal nerve centres. A metabolic action should be substantially non-specific, while – he says – “the different centers within the nervous system react in a very specific way, each one typically different and independent of the others” (ref. 15, p. 472). He then rejects (perhaps in a not entirely justified way, at least with hindsight) the idea that a way to account for the specificity of the central nervous effects “would be to ascribe to each center its own intrinsic, characteristic manner of reaction” (ibidem). Finally he considers also untenable the idea that the central effects can be explained as a consequence of a reflex action, through the activation of sensory fibres, on the basis of the observation that they also persist in embryos in which the sensory fibres have been removed.

Having excluded various possibilities, Hamburger eventually proposes his own interpretation. The stimulus acting on the spinal cord, and responsible for nervous development, is carried by a particular type of sensory fibres that would act as “pathfinders”. These fibres would come into early contact with the corresponding peripheral tissues, and would then somehow transmit the stimulus responsible for growth to the nerve centres.

This is how he puts it:

We must charge the end organs of these first pathfinders with the double task of locating the peripheral field, and, in some way, ‘reporting’ back centrifugally to the central organ the approximate size of the field to be innervated. The fibers would communicate the result of their exploration to their own cell bodies which thus would become the first relay station for the stimulus to be transmitted. Under the influence of the stimuli these nerve cells, which are not yet fully differentiated, when they have sent out their axones, would undergo a morphological or physiological change. (ibidem, p. 475)

In this way the German scientist excludes any chemical action based on a diffusible chemical agent and outlines an explanation which contains in nuce a hint to the axonal transport still to be discovered.

Rita and Levi, the silver impregnation and the obsession with “cell count”.

These are the results and the conclusions contained in Hamburger’s1934 article that, many years later, Rita would qualify of “crystal clarity” for the way it was written, an article that acted soon as a stimulus for her researches in the home laboratory that she was then setting up. In collaboration with Giuseppe Levi, she carried out a series of experiments on the effects of peripheral ablation on the development of the chicken nervous system aimed at verifying Hamburger’s data
and interpretation. There are two main reasons why the reading of this article acted as powerful stimulus for Rita’s (and Levi’s) research. One had to do with the long lasting interest existing in Levi’s laboratory in the themes of the growth of the nervous system and the development of connections between nerve cells, and between these and the tissues innervated by them (muscles, glands, cells of various kinds: see ref. 2). Another – and important one – was that Hamburger’s article was somewhat connected to the neuroembryological research that Rita had been pursuing in collaboration with Visintini. It did not require, however, the sophisticated electrophysiological apparatus available at the Neurological clinics, an apparatus that was absolutely out of the horizons for her home lab.

Rita and Levi studied the problem investigated by the German scientist from a slightly different point of view, and – importantly – with partly different and certainly more effective methodologies. Their approach was nourished by the rich neuro-histological background of Levi’s school, and was based on a severe scientific attitude that the master had followed since his studies at the University of Florence initiated in the last part of the nineteenth century.

In the wake of a long tradition, in order to stain nerve cells, Levi and his collaborators used the metallic impregnation techniques discovered by Golgi in 1873 (and subsequently varied and used with great success by Santiago Ramón Y Cajal and his pupils – including Fernando Castro who had worked in the Levi’s institute in 1934: see refs. 17-18).

Another important attitude that Rita had derived from Levi was the habit of extreme precision in the collection of experimental results and – in particular – the custom of measuring the size of cells and counting their number. Rita is often quite critical, and at times decidedly ironic, about the master’s obsession for the precision of measurements that led sometimes to very boring tasks for his collaborators. Indeed, the first research project, that she and her cousin Eugenia were assigned by Levi, consisted in counting the number of nerve cells of the sensory ganglia in the spinal cord of the house mouse (Mus musculus). The aim was to ascertain whether the number was rather constant or more or less variable (19, see ref. 2).

As one can easily imagine, the work, which required the total count of over three million nerve cells, turned out to be “very tedious”, and certainly did not seem to the two cousins so important as to justify the hard fatigue required. In spite of this, the experience acquired with this research (the basis of the first article published by Rita and Eugenia in 1934, two years before their graduation) will prove to be of considerable importance for Rita in her subsequent research work. On the one hand, the young scientist become acquainted with the method of cell counts and the analysis of variations in the number of nerve cells induced by experimental manipulations. On the other hand, she also became familiar with the study of the sensory ganglia of the spinal cord. Being located outside the spinal cord and well delimited anatomically, these structures are more suitable to quantitative studies than other parts of the central nervous system (as – for instance – the motor columns, studied by Hamburger, which are located inside the grey matter of the cord).

This choice, together with that of the sympathetic ganglia, would prove to be a fundamental resource in the research conducted by Rita in the home laboratory at the time of the war (and also later, in America, in Hamburger’s laboratory). This was because the relatively low and constant number of nerve cells in each single ganglion (and other structural features) would allow for a clear-cut and quantitatively precise assessment of the effects induced by the experimental manipulations of the embryos.

The results of Rita’s and Levi’s experiments in the “laboratory à la Robinson Crusoe”

In all, the experiments, conducted by the two Italian scholars in Rita’s home lab, led, in the period 1942-1945, to the publication of five different articles, three of which authored by both Rita and Levi, and two written in Rita’s exclusive name (refs. 20-24). Due to the racial laws, all these articles appeared in “non-Italian” journals: three of them – dated respectively 1942 and 1943 and 1945 – were printed in the Belgian journal Archives de Biologie. The other two appeared in the scientific journal published by the Pontifical Academy of Sciences (in the Acta or in the Commentationes of the Pontificia Academia Scientiarum). This was possible on the basis of the fact that Vatican City was considered an extraterritorial state with respect to
fascist Italy (“the Pontificia Academia Scientiarum – as Rita wrote many years later – did not discriminate racially”: Levi-Montalcini, 1997, p. 3).

The second of the two texts that appeared in the Commentationes, written together by Rita and Levi, is the most complete as regards the study of the correlation problem stimulated by reading Hamburger’s article (ref. 22). It is dated 1944, although it corresponds to a communication presented to the Academy on February 21, 1943. In 1945, a subsequent article appeared in the Archives de Biologie de Liège, with a main title that is the exact French translation of the previous one, and in the exclusive name of Rita (ref. 24). However, this article was aimed at the analysis of another aspect of the correlation problem, substantially different from that addressed by Hamburger in 1934.

It is interesting to note that the article, which could be the first scientific text to come out of the work done in Rita’s home laboratory, did not directly concern the problem faced by Hamburger in his 1934 publication. This article appeared in the Vatican journal in 1942, exclusively on behalf of Rita, a circumstance that might suggest that the research work, on which it was based, had been carried out before Levi joined the domestic laboratory (ref. 20).

The topic addressed by Rita in this first work was that of the neurogenesis, in the chicken embryo, of the accessory nucleus of the abducens nerve (the sixth pair of the cranial nerves). The development of the cranial nerves was a indeed a theme already present in Levi’s school, and – in particular – it had been the subject in 1921 of a research by Tullio Terni, the first of Levi’s pupils. Analysing Rita’s bibliography in the early years of her career, up to the beginning of the American period, it is quite evident that the neurogenesis of the cranial nerves was the long-term research program she had planned for her work in the Anatomical Institute of Turin, in the period preceding the promulgation of the racial laws.

Before describing and discussing in detail the experiments on the “correlation” reported in the papers by Rita and Levi in the period 1942-1945, it is necessary to emphasize the truly “extraordinary” nature of the research activity of the two Italian scientists in this period. It was a time when most people – and Jews in particular – were almost uniquely absorbed by every possible effort to save their lives in the face of dangers and immediate threats, while the whole world around them seemed to collapse. On their side, Rita and Levi were totally absorbed in scientific problems that probably seemed rather trivial to those around them (and perhaps sometimes to themselves).

Surprising was also the fact that in a condition in which any type of activity was difficult, and in particular the scientific one, the two scholars were able to carry out “at home” experiments that required a rather sophisticated apparatus. Their research needed also an effort of organization that was not exactly simple in those difficult periods. In particular, in conditions of great food shortage a not easy problem was that of obtaining the fertilized eggs necessary for the investigation. It is worth remembering here that in Bremer’s laboratory in Brussels, one of the best equipped physiology laboratories in the world, Rita had failed, because of trivial technical problems (as the malfunctioning of a thermostat), to keep her embryos alive. Now she was able to conduct a difficult research on these same preparations, in very difficult circumstances (truly comparable to those in which the legendary hero of Defoe had found himself on a remote and wild American island).

Another surprising element was that two scientists whose names clearly indicated their Jewish ancestry could publish articles in journals printed in Belgium during the Nazi occupation.

As already mentioned, unlike Hamburger and – before him – Shorey, who had studied mainly the motor columns of the spinal cord – in their research on neurogenesis in the chicken embryo published in the period 1942-1945, Rita and Levi focused their attention especially on the sensory spinal ganglia. In particular, they chose a particular ganglion, the one corresponding to the 25th segment (i.e. that in the centre of the group of segments responsible for the sensory innervation of the hind limb). As they pointed out, in particular in their 1944 article, this procedure was essential, because, in the case of spinal motor neurons, investigated by Hamburger and Shorey, it was impossible to study the modifications induced by experimental manipulations with a rigorous quantitative method. In the ganglia, on the other hand, it was easy to do this, for anatomical reasons (their anatom-
ical individuality and separation from the medulla), in particular if an adequate method of staining was used (such as the silver impregnation of Cajal-De Castro that Rita knew very well).

With this long-standing and glorious method it was possible to distinguish neurons, in the various stages of their differentiation, from undifferentiated cells and from supporting (or other non-nervous) elements. This was mainly because of selective staining of neurofibris, which were not detected by the methods based on haematoxylin used by Hamburger and Shorey.

Another important problem and source of fundamental differences with the results of the two Italians was that Hamburger (and Shorey before him) had limited his study of the spinal cord to a very short, and rather late, period after the experimental ablation. Because of this, the previous authors could not detect the initial modifications induced by the extirpation of the peripheral tissue, modifications which – in the hands of Rita and Levi – proved to be of fundamental importance for clarifying the mechanisms underlying the embryonic development of the nervous system.

Some of the experiments of the two Italian scholars were also conducted on sympathetic ganglia. In addition to allowing, as we have said, a more rigorous study of the effects of experimental manoeuvres, these choices will prove, in retrospect, very fortunate, because the sensory and sympathetic ganglia of the spinal cord are the privileged target of NGF (then still to be discovered).

The main “discrepancy” with respect to previous studies, and in particular to that of Hamburger, which emerged from Rita’s and Levi’s researches concerned the initial effects induced by the ablation of peripheral structures on the development of nerve sketches. According to the conceptual framework to which Hamburger was referring, the ablation of the limb buds should have caused a lack or reduced development of the corresponding nervous structures, because the lack of a stimulus capable inducing the growth of the nerve centres responsible for their innervation. As mentioned Hamburger described his results as effects of reduced growth, or hypoplasia.

In their study Rita and Levi instead observed that, after the ablation of a peripheral structure (usually the bud of the hind limb of one side removed of the third day of incubation – the bud of the other side being left normal for control), there was initially normal growth of the ganglion cells responsible for their innervation. Indeed, at the initial stages there no significant difference between the operated side the control side. In fact, there was therefore no evidence of the reduced proliferation that should have occurred in the absence of the hypothetical growth-inductive action of the peripheral tissue.

Only in the most advanced stages of embryonic development (starting from the sixth day of incubation, that is, three days after ablation), Rita and Levi observed a significant decrease of nervous elements. However, this phenomenon – far from being caused by a reduced development of the nerve centres – appeared to be the consequence of a profoundly different (and somewhat unexpected) process, hard to reconcile with the existing theories. It was the effect of a degeneration, in some way secondary, which involved nerve cells already adult and differentiated (that is, rich in neurofibris, and which had already emitted the process intended to form the neurite - this was term used to designate the axon designated as “neurite” by Rita and Levi). These adult-type cells progressively lost their specific characters, while the undifferentiated nerve elements continued their proliferation and growth at a substantially normal rate. The phenomenon became more and more accentuated with the passing of days, to the point that in the advanced stages, the proportion of differentiated neurons compared to those without signs of differentiation (i.e. without fibrils and neurites) changed by about 20 percent between the injured side and the control side.

Based on their experiments Rita and Levi came to the following consideration:

During the first period, the development of the centres is not altered at all. Moreover, the reduction in the number and size of sensory neurons, differentiated with neurofibrils and provided with neurites, begins to occur only after that the neurites of these neurons have reached a certain length and cannot, due to the ablation of the bud, reach the peripheral organs for which they are intended (receptors of the skin of the muscles). It seems therefore probable that the dis-
appearance of a considerable number of neurons and the reduction in the size of other neurons (and also the atrophy of well-differentiated neurons) observed in our experiments can be explained by the absence of normal synapses at the level of peripheral neurites. (ref. 21, pp. 544-545).

In other words, after the peripheral ablation, the centres of the spinal cord that in the course of normal development are destined for their innervation (sensory or sympathetic ganglia) develop normally in an initial phase, as if they were not affected at all by the absence of the target organs. Only subsequently do they undergo a phenomenon of degeneration. The presence and regular development of the peripheral target structures operate apparently in such a way as to maintain the normal condition of the fully mature cells, preventing, in the late phase of embryonic growth, their degeneration. That is, they do not work, as supposed by the previous authors – and in particular Hamburger – by producing, in the initial phases, an inductive stimulus factor necessary to favour their multiplication and differentiation.

In the résumé of their article, the two Italian scientists summarize their results by saying that “from the count of less differentiated [nerve] cells, carried out both on the control side and on the operated one, it appears that, in all stages, the number is approximately the same on both sides”. Against the interpretation of previous authors (Shorey and Hamburger) they conclude with this rather peremptory statement: “the hypothesis advanced, according to which cell multiplication is regulated by the peripheral field, has not been supported by our research”. (ibidem, p. 545)

The article in extenso of 1944, published in the Vatican Commentationes was based on a large number of experiments, each of which involved the counting of a number of nerve cells varying between 500 and 1000 elements, and the measurement of their size. It came again old Levi’s obsession with counting and measuring, performed at various stages of development and with a rigorous chronological sequence (which usually caused the bad mood of internal students and collaborators). Furthermore, the results were summarized and illustrated with extensive use of tables and graphs, this also being a characteristic of Levi from his early years.

The conclusions of the 1942 work were strengthened and clarified, based on an experimental effort that would have appeared “heroic” in any circumstance, but which was even more impressive due to the decidedly exceptional conditions in which it was performed (a home laboratory, operated by two Jewish scholars, at the time of the racial persecutions):

Only the differentiated neurons in which neurofibrils have formed and neurites have appeared, regress due to the lack of the limb; the regression begins 70 hours after the operation, thus coinciding exactly with the moment in which the neurites, if development had proceeded undisturbed, would have reached the terminal organs of the limb. (ref. 23, p. 556).

Rita and Levi summarized their interpretation with this statement:

The absence of the limb therefore does not inhibit the multiplication of undifferentiated cells, nor the specific differentiation of these into neurons, both in early and later periods; the tendency to differentiate is a property inherent in the elements of the nervous centres, because it is transmitted to them in a hereditary way. On the other hand, when the neurites of neuroblasts grown in length are unable to grow further and to make normal connections with the peripheral elements of the teguments and muscles, the regressive process begins both in the pyrenophore [i.e. the cell body] and in the neurites. (ibidem, p. 558)

As mentione, the conclusion of the two papers by Rita and Levi represents what could be considered a real paradigm shift in the history of neuroembryology. From an inductive paradigm, in which the peripheral tissue (to be innervated), induces the proliferation of precursors of nerve cells and stimulates their differentiation, we pass to a paradigm of a different type, based on the idea of growth of nerve centres independent of their target peripheral organs. The intervention of an action originating from peripheral structures would occur only at a later stage, and would serve to maintain the condition of mature nerve cells, already grown, preventing their degeneration.

The idea of an embryonic development that implied, during its normal course, a mechanism of de-
generation - in some way programmed - was definitely outside the conceptual schemes of the time. Growth was seen as the fundamental expression of life, and the phenomena of degeneration and loss of living substance were considered only accidental and random processes. The idea that nerve cells were somehow programmed to die, even before the death of the organism, and that they were preserved from this “physiological” death through the action of peripheral structures, was certainly a great biological novelty. It contained – albeit in the background and in a still unclear way – a truly revolutionary principle that anticipated the times, and which will be fully understood many years later with the studies on apoptosis, or programmed cell death.

It should be noted here that, in both in the 1942 and in the 1944 article, in interpreting their results, Rita and Levi excluded any intervention of chemical factors (of the type supposed by Shorey). In their idea, to be responsible for the late degeneration of differentiated neurons would instead be “the impossibility of growing further and contracting normal connections with peripheral elements”. This “connectivistic” conception was more in line with what Rita had glimpsed in her research a few years earlier together with Visintini. As we have already said, the two young scholars had observed that some terminations of the vestibular fibres, unable to form normal synapses, underwent degenerative phenomena that resembled the bolas observed many years earlier by Cajal in different circumstances, but always in relation to degenerative phenomena (see ref. 1).

In a narrative of the beginnings of her research published in 1997 Rita writes that it was she who actually supported the hypothesis “that the inability of sensory neurons to establish synaptic contacts with their target organs was responsible for the massive death of these cells” (ref. 25, p. 3).

The idea of a chemical factor (as anticipated by Shorey in 1909) will surface later in Rita’s research. This would occur during the first period of her work together with Hamburger in St. Louis. A long time would be necessary, however, to assert it with certainty. Some crucial experiments performed by the Italian scientist in America, together with her collaborators, and in particular Stanley Cohen, will show beyond any doubt that is indeed a diffusible chemical agent the factor responsible for the preventive effect of neuronal degeneration, exerted by peripheral tissues on the development of the nerve centres. This agent, which will be shown to be also produced by structures very different of the embryonic limb buds (including some tumours, the venom organs of some snakes, and the salivary glands of some animals), was eventually identified by Rita and Stanley Cohen and finally named Nerve Growth Factor (NGF, as we know). Synthesized in the course of development by some peripheral tissues waiting to be innervated, the NGF is transported in a retrograde way to the cell body where it acts through a complex series of chemical events whose identification has marked the opening of an entirely new field of modern biology (refs. 5, 25 and 27).

The mysteries of the letter from America, and the a posteriori narration.

As repeatedly mentioned, due to a series of complex and rather fortuitous circumstances, the experimental differences between the results obtained in the home laboratory and those reported in the 1934 Hamburger’s paper ended up constituting one of the most important turning points in Rita’s scientific career. This happened in particular because these articles came to the attention of Hamburger, arousing his keen interest in the results reported by the two Italian scholars, to the point of inducing him to invite Rita to America, in order to continue his research in his laboratory in St. Louis.

According to Rita’s recollections, Hamburger had the opportunity to read both the short article published (in 1942) in the Belgian Archives de Biologie, and the paper in extenso appeared (in 1944) in the Vatican journal (written respectively in French and Italian, the second with an abstract in Latin, both in the name of Rita and Levi) (see ref. 25, p. 3). Neither periodical was (nor is it at the time this article is written) in the library of Washington University. From the letter Hamburger sent to Levi on July 8th, 1946, we learn that he received the article through the Italian ambassador in Washington (probably some embassy official informed Hamburger that Levi had returned to his Turin Institute at the end of the most dramatic phase of the war).

In the Hamburger’s letter (originally written in German, but translated by himself into English at a
much later date), the German-American scientist mentions his own initial and unsuccessful attempts to reach Levi. He writes that the previous year (namely in 1945) he had sent a letter with the reprints of some of his publications to an address in Florence indicated by “Dr. Luria” (i.e., Salvador Luria, that is Rita’s colleague emigrated - as we know - to America in 1940 as a result of the racial laws), but – he adds – “everything was returned to me as undeliverable”.

In the 1946 letter, Hamburger does not specify how many and which articles published in previous years by Levi and Levi-Montalcini he had received, but it is likely that he received them all. This is because, in discussing the concordances and discordances between his own experiments and those of the Italian colleagues, he cites an experiment involving a brain stem lesion which is reported and discussed in the last article of the series, namely the one published in 1945 in the Belgian magazine, in the exclusive name of Rita.

In a conference on Giuseppe Levi held in Turin in May 2019, one of Rita’s pupils, Antonino Cattaneo, has pointed the attention on a rather intriguing aspect of the 1946 letter to Levi. This is the passage where Hamburger insists on the fact that, because of the time required to verify their respective results, Rita should stay in his laboratory for at least one year or two. This contrasts with most of Rita’s memories in which the scientist says she was invited for a period of six months. Only in a few circumstances, Rita speaks of a longer period (one year), and in a video recording produced in 2000 he even said that she was “invited for three months” (see ref. 28).

Life events would “dramatically” change this initial perspective on length of stay in the United States, and Rita would spend many years of her long life in America, working in the Department of Zoology at Washington University in St. Louis. For about 25 years, she will stay there without interruption, and then, until the 1980s, she will spend half the year in St. Louis and half in Rome, where she was initially granted a laboratory, by the Istituto Superiore di Sanità (ref. 27).

Alluding to a considerably shorter period, Rita was probably transposing to the contents of Hamburger’s letter what at the time was her idea of the length of her stay abroad; and also the wishes of her family, who – as we know – even in earlier occasions, was averse to a long separation from the young woman.

A clue as to the reasons for Rita’s distorted memory comes from the consideration that at that time there was a strong sentimental interest in her on the part of a classmate, Guido. Guido was the friend who – as she narrates in the Elogio – used to walk with her along the avenues of the Valentino Park of Turin, and drove her on motorbike to the hills around the town (he was the same Guido in the episode of the reading of Hamburger’s 1934 paper).

When Rita was invited by Viktor Hamburger to

Figure 11. Rita Levi-Montalcini in a photo of 1948, at the gardens of the Marine Biological Laboratory of Woods Hole (© Piera Levi-Montalcini).
go to St. Louis to conduct experiments on the development of the nervous system, the friendship with Guido (seen with some suspicion by the girl’s family especially for the swaggering nature of the young suitor), imposed a choice on Rita. According to a version of which there are traces in family memories, the departure should serve to verify – with the programmed separation of some months – the strength and seriousness of the love bond between the two young people. Hamburger refers to a slightly different version, but always based on the existence of a suitor, in a private manuscript written in May 1989, entitled “The Queen and I”. In the first part of this text, which bears the subtitle “Rita - Enigma?”, Hamburger writes, undoubtedly based on what Rita herself had said: “one of the reasons for her avid acceptance of my invitation to come to St. Louis in 1946 was to escape from a suitor”.

Whatever it is, probably the relation with Guido was, for one reason or another, one of the factors that pushed Rita, generally reluctant to leave her family, to face the scientific emigration journey to the new continent in 1947. By saying that she had been invited for a period of six months (or even less), probably she was transposing to her recollections what was - at the time - idea about the length of the staying in St. Louis (and not the actual one-two years period indicated as necessary by Hamburger).

This distorted recollection by Rita on the prospective duration of her America sojourn might appear of relatively trivial importance. Certainly more relevant is the fact that, in all probability, the research conducted with Levi in the legendary home laboratory became truly fundamental for Rita (and such as to condition her entire scientific career and her life) only in retrospect, and only because of the extraordinary developments of the St. Louis period.

Let’s try to see what clues exist to support this hypothesis.

If Rita and Levi had immediately sensed the revolutionary aspect of their discoveries in the war period, there would be little doubt that, at the time of the resumption of the ordinary experimental activity in the Anatomical Institute, they would have promptly dedicated themselves to the continuation of this type of research. Especially Rita, a young scientist and certainly less burdened by the commitments that certainly lay over Levi, who was then reorganizing the research activity in his Institute and resuming the teaching activity in the Faculty of Medicine.

This did not happen. In the after-war period, the publications of Rita (who had found an institutional collocation in the “Study Center on the growth and senescence of organisms” newly created in Turin, on the initiative of Levi, by the Italian National Research Council) were all dedicated to the study of the development of the cranial nerves. As said, this was a traditional line of research of Levi’s group, to which Rita had devoted herself in the last period she spent in the Anatomical Institute in the pre-war period. It had also been – as we have noted above – the subject of the first research performed in 1940 in the home laboratory, and the argument of her first publication appeared in 1942 in the Vatican Acta.

In the period 1946-1947 Rita in fact published seven scientific articles (mostly short notes presented by Levi at the Accademia dei Lincei, but also an article in extenso, in collaboration with Amprino, in the Belgian Archives de Biologie; see refs. 29-34). Six of them were dedicated to the origin and development of the cranial nerves, and one concerned the sympathetic thoraco-lumbar system. Although in one of these researches Rita intervenes in the embryo with the removal of the mesencephalic vesicle, none of these articles clearly takes up the themes that had been the focus of research in the home laboratory during the war period.

Even the first article of the St. Louis period, which appeared in 1949 and was signed solely by her, Rita focuses on the theme of cranial nerves. It concerned the development of the acoustic–vestibular system and was a direct continuation of the research on the auditory system carried out in Turin, in the immediately post-war period (ref. 35). However, this article also addresses the “theme of correlation”, which Rita had begun to study in the home laboratory, and which will then be at the centre of her research with Hamburger, marking the resumption of the journey of the NGF. It is no coincidence, however, that, in this 1949 article, Rita appears with the double affiliation, as a member of both the Turin Institute of Anatomy and the American Department of Zoology, a fairly probable indic-
ation that part of the research was done in Turin. This idea is supported by a passage from the second part of the private Memorandum, written in manuscript form by Hamburger in 1989, with the subtitle: “The Years of Collaborations (1947-1953)”: 

Hamburger writes about Rita:

She brought with her the microscope sections of a large amount of material of early embryonic otocyst extirpation in which the effects of the operation on the cochlear and vestibular centers were to be studied. I suppose she had studied this material already, but I don’t remember if she brought with her protocols, notes or pictures. At any rate, not being familiar with neurology, I had to learn all about the nucleus angularis, magnocellularis, laminaris, etc., and I worked extensively with her on the slides (Hamburger, 1989, p. 12)

With reference to the last sentence of this quo-
tation, it is interesting to note here en passant that, as it had occurred with Levi in the home laboratory, also in this case Rita acted as the chief investigator, with a famous scholar as her assistant.

All this outlines a substantial picture of continuity between the research conducted by Rita between the period immediately preceding and that following the war. We are thus induced to suppose that at the time she did not perceive the revolutionary scope of the research in her laboratory “à la Robinson Crusoe”, and all became truly revolutionary, and epic as well, only in retrospect, after the NGF discovery.

To what should we attribute this? To a scarce in-sight of Rita?

Difficult to think of such a thing for a person of Rita’s intelligence and astuteness, able (as often she says, even in private letters) as few to understand the importance of the results, and to identify the directions in which to pursue her research, endowed as she was with a special flair for the big scientific “truffles” (see ref. 2).

In fact, in themselves, the experiments with Levi during the war period, although undoubtedly stimulating and useful in demonstrating the groundlessness of some previous hypotheses on the mechanisms of embryonic development of the nervous centres, were revolutionary only a posteriori, on the basis of evolu-
tions then difficult to foresee.

Apparently in contrast to what previously said, they could, instead, be “accommodated” within the context of relatively consolidated scientific concepts, on the basis of certain considerations. At the time, it was well known that, even in the case of humans, congenital atrophy of a limb often involved a reduced development of the motor centres responsible for its innervation. Also known was that even the simple physiological inactivity could involve – on both on the motor and sensory fields – a more or less marked atrophy of the corresponding nervous structures. On those grounds, it should not therefore appear so surprising that there was a degeneration of the nerve fibres and cells after ablation of the corresponding peripheral structures. This is because, following the extirpation of the limb, both the correct anatomical relationship between nerve fibres and peripheral tissues to be innervated (on both}

Figure 12. Viktor Hamburger and Rita Levi-Montalcini in their mature age (© Piera Levi-Montalcini).
the sensory or motor side) were missing, and consequently the functional stimulus acting on the nerve cells was reduced or abolished. This was a particularly easy possibility to suppose for Rita and Levi, because of their supposition that the element responsible for nervous trophism was, not so a chemical agent released from peripheral tissues, but a correct synaptic relationship between the nerve fibres and their targets.

The perspective will totally change, when the chemical nature of the trophic agent involved in these experiments becomes clear. This will happen especially with the “casual” discovery of some mice with a particular type of tumour capable of inducing effects similar to those of the mysterious peripheral agent; and with the experiments conducted with explants of this tumour on cultured cells. And then with the demonstration that the injection of a tumour extract into the allantoidal cavity of the embryo was able to produce an extraordinary growth of cells and nerve fibres throughout the organism, in the absence of any direct contact between tumour cells and tissues peripheral. A result that, among other things, also excluded the viral nature of the agent (taken into consideration at a certain point), and brought materials to support its physiological action during normal development. And finally, along this line, the “immuno-sympathectomy” experiments, that is, the suppression of the growth of the sympathetic system induced by the administration of antibodies against the agent yet to be identified in its precise chemical structure (see refs. 26 and 28).

All this was contained in nuce in the results obtained in the small home laboratory, by the young scientist and the elderly teacher, but not even a very perspicacious “truffle dog” like Rita could then understand the extraordinary significance that those results contained in perspective.

What will happen next, in the St. Louis period, will also change the memory of all this, and will give this extraordinary woman, also gifted with considerable literary talent, the opportunity to narrate with vivacity and charm things that could have been lost in the river of forgotten memory. As the article read on the cattle cars train slowly advancing in the Turin countryside, on a rather ordinary day, destined years later to be remembered as fateful.

History, as we know, is how it is told. For this reason, in order to have a proper and wider perspective of the events that have really taken place, those events should be narrated and discussed not exclusively by those who have experienced it first-hand.

This is what I have endeavoured to do in this article.

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